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REVIEW

A Review of Romiplostim Mechanism of Action and Clinical Applicability

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Abstract: Thrombocytopenia results from a variety of conditions, including radiation, chemotherapy, autoimmune disease, bone marrow disorders, pathologic conditions associated with surgical procedures, hematopoietic stem cell transplant (HSCT), and hematologic disorders associated with severe aplastic anemia. Immune thrombocytopenia (ITP) is caused by immune reactions that accelerate destruction and reduce production of platelets. Thrombopoietin (TPO) is a critical component of platelet production pathways, and TPO receptor agonists (TPO-RAs) are important for the management of ITP by increasing platelet production and reducing the need for other treatments. Romiplostim is a TPO-RA approved for use in patients with ITP in the United States, European Union, Australia, and several countries in Africa and Asia, as well as for use in patients with refractory aplastic anemia in Japan and Korea. Romiplostim binds to and activates the TPO receptor on megakaryocyte precursors, thus promoting cell proliferation and viability, resulting in increased platelet production. Through this mechanism, romiplostim reduces the need for other treatments and decreases bleeding events in patients with thrombocytopenia. In addition to its efficacy in ITP, studies have shown that romiplostim is effective in improving platelet counts in various settings, thereby highlighting the versatility of romiplostim. The efficacy of romiplostim in such disorders is currently under investigation. Here, we review the structure, mechanism, pharmacokinetics, and pharmacodynamics of romiplostim. We also summarize the clinical evidence supporting its use in ITP and other disorders that involve thrombocytopenia, including chemotherapy-induced thrombocytopenia, aplastic anemia, acute radiation syndrome, perisurgical thrombocytopenia, post-HSCT thrombocytopenia, and liver disease.

Keywords: immune thrombocytopenia, pharmacokinetics, pharmacodynamics, structure, thrombopoietin receptor agonist

Introduction

Thrombocytopenia can occur because of a variety of conditions, including autoimmune disease, bone marrow disorders, hematologic disorders associated with severe aplastic anemia, chemotherapy, radiation, pathologic conditions associated with surgical procedures, and hematopoietic stem cell transplantation (HSCT).[1] It is well known that thrombopoietin (TPO) plays a critical role in platelet production and other hematopoietic pathways.[2] TPO receptor agonists (TPO-RAs) make an important contribution to the management of immune thrombocytopenia (ITP) by increasing platelet production and therefore reducing the need for other treatments or platelet transfusions.[3] While the mechanism(s) of action of TPO-RAs center around increasing platelet production, these agents may play a larger role in the host.

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Development of early (first-generation) TPO-RAs (eg, PEGylated megakaryocyte growth and development factor) was eventually discontinued because of neutralizing antibodies that cross-reacted with endogenous TPO.[4] As a result, the second-generation TPO-RAs, such as romiplostim, eltrombopag, and avatrombopag, were developed with the goal of avoiding these cross-reacting immune responses.[4]

Romiplostim is a TPO-RA that has been used in adults with chronic ITP for more than 11 years. Use of romiplostim was recently approved in pediatric patients in the United States and the European Union, and use in adults has been extended to include those with newly diagnosed ITP.[5,6] The efficacy of romiplostim in severe aplastic anemia, chemotherapy-induced thrombocytopenia, and several other thrombocytopenic disorders is currently under investigation.[1] Here we review the mechanism of action and efficacy of romiplostim for the treatment of thrombocytopenia in various diseases.

TPO Signaling and Mechanism of Action

As reviewed by Kuter and Begley,[7] TPO is synthesized primarily in the liver as a single 353–amino acid precursor protein. Cleavage of the N-terminal 21–amino acid signal peptide reveals a mature molecule comprising two domains: a receptor binding domain and a highly glycosylated carboxy-terminus important for protein stability (Figure 1).[7,8] TPO itself has been shown to be the most important growth factor for platelet production[2,9] because it is involved in virtually all stages of platelet production from stem cell through mature megakaryocyte (and possibly platelet release).[10,11] Plasma concentrations of TPO increase in response to a decline in platelet mass, especially if megakaryocyte numbers are reduced. Conversely, when platelet levels are high, TPO binds to its myeloproliferative leukemia virus (MPL) receptors on circulating platelets or megakaryocytes in the bone marrow (Figure 1).[11] TPO has been

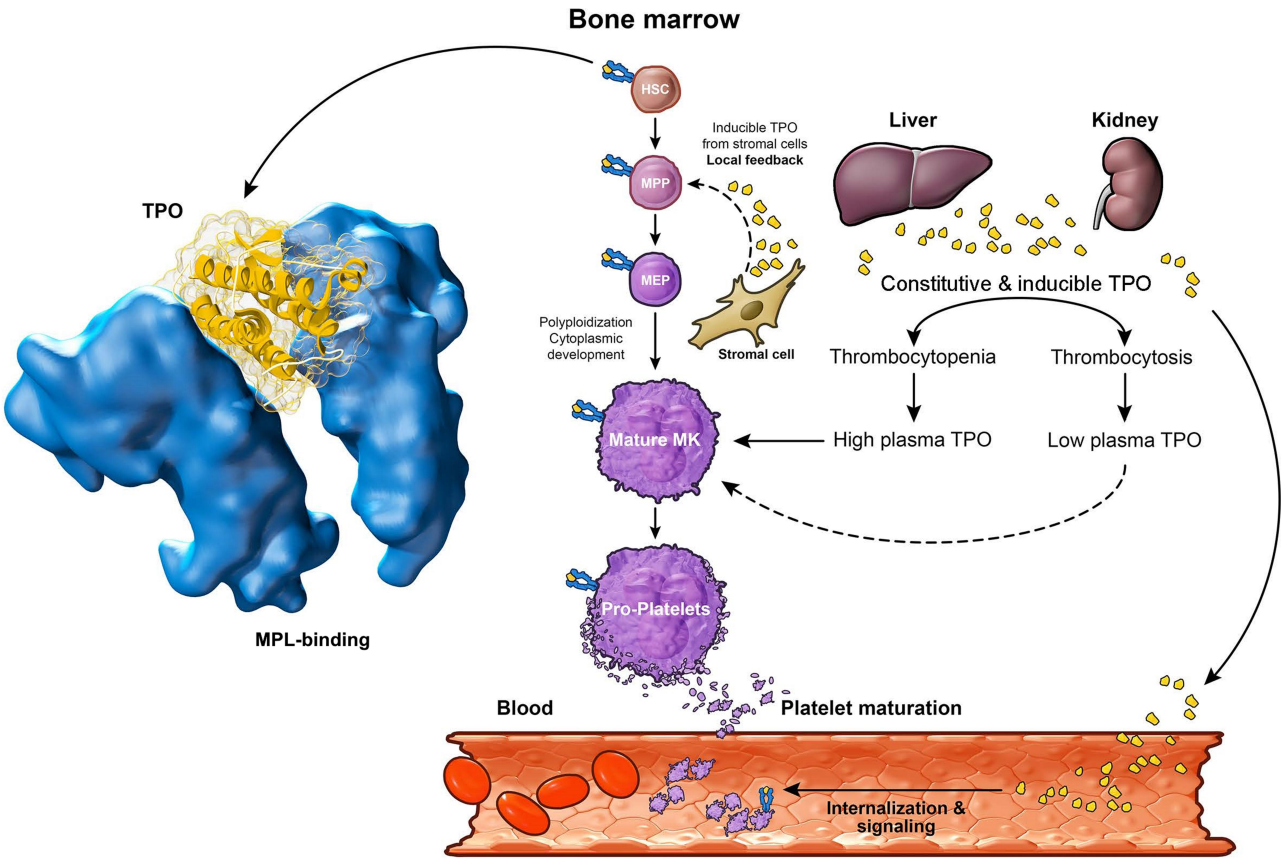

Figure 1 Structure of thrombopoietin[7,8] and TPO-MPL signaling.[11] Thrombopoietin is synthesized in the liver and kidney as a single 353-amino acid precursor protein. Plasma concentrations of TPO increase in response to reduced platelet mass. Conversely, TPO binds to MPL receptors on circulating platelets in the blood when platelet levels are high. Upon exogenous TPO stimulation, HSCs differentiate to megakaryocytes. Local TPO production by stromal cells in the bone marrow also stimulates megakaryocyte maturation.

Abbreviations: HSC, hematopoietic stem cell; MEP, megakaryocyte-erythroid progenitor; MK, megakaryocytes; MPL, myeloproliferative leukemia virus; MPP, multipotent progenitors; TPO, thrombopoietin.

shown to increase the size, ploidy, and number of megakaryocytes[12,13] and stimulate expression of platelet-specific markers.[12,14] When combined with other growth factors, TPO has a synergistic effect on the growth of myeloid and erythroid precursors[15–17] and stimulates trilineage responses when used alone in severe aplastic anemia.[18,19] In hematopoietic stem cells, stimulation of the TPO receptor (TPO-R) results in signaling that influences quiescence, self-renewal, proliferation, and differentiation to megakaryocyte progenitors.[11] TPO also affects genome stability (through ERK- and NF-κB–mediated activation of *Iex-1* to promote DNA-protein kinase-dependent nonhomologous end-joining repair[20]), mitochondrial metabolism, and potentially iron metabolism in hematopoietic stem cells. In addition, TPO alters hematopoietic stem cell lineage differentiation via metabolic regulation. In turn, these functions may affect the outcome of TPO-MPL signaling in hematopoietic stem cells,[11] areas in which TPO-RAs have unique and distinct effects.[11] Along with increasing platelet production, TPO-RAs also appear to transiently extend their circulating life span, potentially via signaling through the AKT pathway and reducing sensitivity to apoptotic stimuli.[21]

Mechanisms of ITP

Platelet life span is reduced in patients with ITP.[22] Although the pathophysiology of ITP is not completely understood, evidence suggests it is a disease of platelet destruction and insufficient platelet production (Figure 2).[23–26] The contribution of these pathologic mechanisms in individual patients is uncertain, but it is thought that antibodies and T cells affect both platelets and megakaryocytes. For example, insufficient megakaryopoiesis[23,25] and impaired proplatelet formation[27,28] have both been described as potential mechanisms leading to thrombocytopenia. Common mechanisms involved with platelet clearance include antibody and T-cell–dependent immune mechanisms, platelet apoptosis, and glycan modifications.

In patients with ITP, it has been proposed that anti-glycoprotein IIb/IIIa (GPIIb/IIIa) autoantibody-coated platelets are targeted for destruction by macrophages through one of the following: activation of fragment crystallizable (Fc) γ, a process that is controlled by spleen tyrosine kinase and results in phagocytosis by macrophages or complement pathway receptors.[29–32] Platelet antigens are thought to be presented by major histocompatibility complex class II antigens on the surface of the macrophages, thus stimulating autoreactive T cells.[26] It is thought that the T-cell response is skewed toward activation of type 1 T-helper (Th1) and type 17 T-helper (Th17) cells, reduced regulatory T-cell (Treg) activity, and increased cytotoxic T-cell activity, with the latter possibly destroying platelets or inhibiting production by megakaryocytes.[33–39] Additionally, platelet glycoprotein autoantibodies may inhibit megakaryocyte maturation.[23,25,31]

Approximately 70% of patients with chronic ITP have detectable serum autoantibodies that generally target GPIIb/IIIa and/or GPIbIX;[40–42] however, some patients with ITP have no detectable autoantibodies, yet their disease presentation is similar to those with antibodies. The presence of autoantibodies is not always associated with active disease.[40,42] In these patients, cell-mediated immune mechanisms, such as CD8+ cells in bone marrow, might suppress megakaryocyte apoptosis, leading to impaired platelet production and thrombocytopenia.[36,43,44] Platelets can present antigens to CD8+ cells, indicating that they may also participate in the initiation of acquired immune responses in addition to supporting and promoting acquired immune responses.[45] This characteristic of platelets is thought to arise from megakaryocytes.[46] Evidence also suggests a role for increased classical pathway complement activation in ITP.[47]

Platelet survival is controlled by an intrinsic apoptotic program. The antiapoptotic protein Bcl-xL constrains the proapoptotic proteins Bak and Bax to maintain platelet survival; as Bcl-xL degrades, older platelets are primed for cell death.[48,49] Genetic inactivation or pharmacologic inhibition of Bcl-xL leads to Bax-/Bak-induced mitochondrial damage and promotes the apoptotic cascade, reducing platelet half-life, and causing thrombocytopenia.[48,49] Imbalanced expression of Bcl-xL and Bax has been associated with platelet apoptosis in ITP.[50]

Another method of platelet clearance appears to involve glycan modifications on platelet surface proteins, which may be triggered by the loss of terminal sialic acid residues on platelet surface glycoproteins as they age. B cells secreting anti-GPIb or anti-GPIIb/IIIa antibodies have been detected in plasma and are a hallmark of patients with ITP.[51] These antibodies to GPIbα, among other mechanisms, can also lead to neuraminidase-mediated desialylation. Loss of the terminal sialic acid residues triggers recognition and uptake by the Ashwell-Morell receptor.[49,52] Uptake of the desialylated platelets stimulates JAK-STAT signaling and upregulation of TPO mRNA expression by the same pathway as interleukin (IL)-6 in hepatocytes, leading to increased serum TPO levels and subsequent increase in megakaryopoiesis and platelet biogenesis.[52–56]

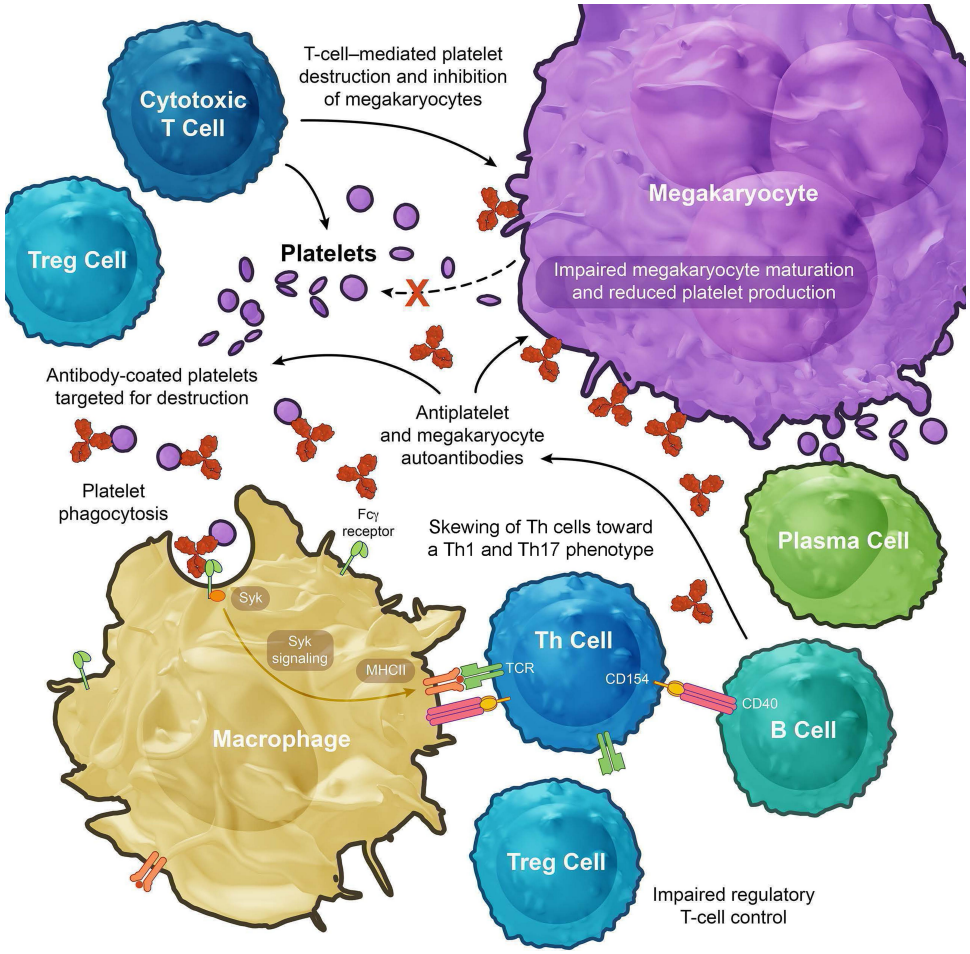

Figure 2 Pathophysiology of immune thrombocytopenia.[26] Production of antiplatelet autoantibodies appears to be a key event in the pathophysiology of ITP. These autoantibodies target platelets for destruction by macrophages in the spleen or liver through activation of Fcγ receptors, a process controlled by spleen Syk. Autoantibodies may also destroy platelets through other mechanisms and inhibit platelet production by megakaryocytes. Antigens from phagocytosed platelets are thought to be presented by the MHCII to TCRs, stimulating autoreactive T cells. Pathogenic T-cell changes seen in ITP include skewing of T-helper cells toward a type 1 T-helper (Th1) and type 17 T-helper (Th17) phenotype, reduction of regulatory T-cell activity, and an increase in cytotoxic T cells. From *N Engl J Med*, Cooper N, Ghanima W. Immune Thrombocytopenia. 381(10):945–955. Copyright ©(2019) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[26]
Abbreviations: CD, cluster of differentiation; Fcγ, fragment crystallizable; ITP, immune thrombocytopenia; MHCII, major histocompatibility complex class II; Syk, tyrosine kinase; TCR, T-cell receptor; Th1, type 1 T-helper; Th17, type 17 T-helper; Treg, regulatory T cell.

Overview of the Structure, Mechanism of Action, and Pharmacokinetics/ Pharmacodynamics of Romiplostim

Romiplostim is a peptibody comprising four TPO-R binding domains (identified by screening mutagenesis peptide libraries[57]) with high affinity for the TPO-R (MPL) and one carrier Fc domain[4,5,58,59] and has no sequence homology with endogenous TPO (Figure 3).[4,58,60] Romiplostim binds to and activates the TPO-R on megakaryocyte precursors in bone marrow.[58] It binds in the same manner as endogenous TPO and can displace TPO from its receptor.[3,59] Romiplostim activates many of the same pathways as TPO, leading to sustained improvement of platelet counts with continued treatment in patients with ITP.[61–64] Preclinical and clinical data suggest that romiplostim also has immunomodulatory effects.[65,66]

One study in mice suggested that romiplostim not only significantly raised platelet counts but also lowered anti-platelet antibody levels.[66] In humans, romiplostim was shown to improve in vitro Treg function in patients with chronic ITP. Although the mechanism behind Treg normalization is unclear, it is hypothesized that this is caused by the increased plasma levels of transforming growth factor-beta resulting from increased platelet turnover secondary to increased platelet production.[65]

Much less is known about the effects mediated by the Fc region of the molecule and any immunomodulatory effects that may occur by specifically binding with Fc

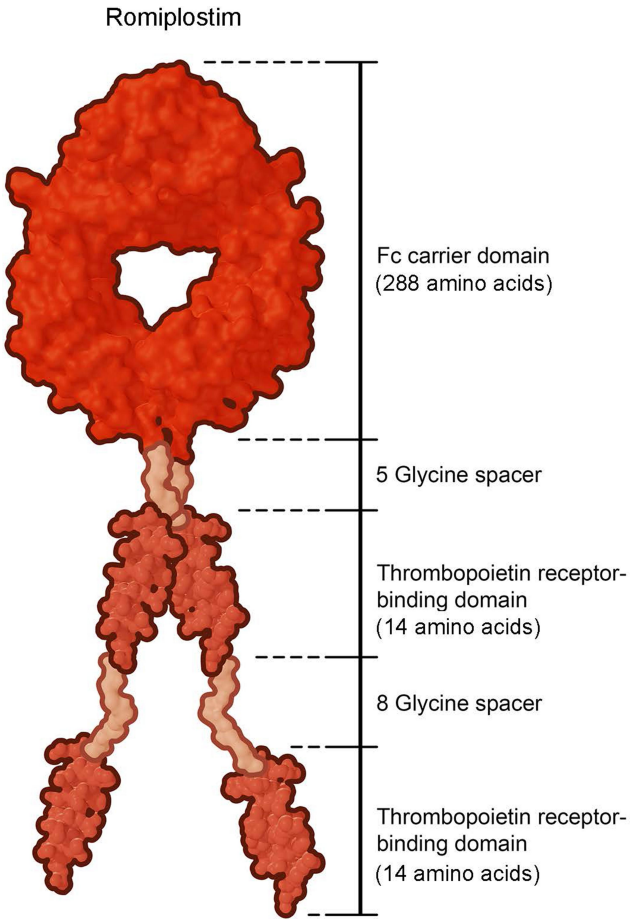

Figure 3 Chemical structure of romiplostim.[60] Romiplostim (molecular weight ≈60 kDa) is a peptibody composed of four identical thrombopoietin peptides of 14 amino acids each that are chemically coupled by glycine spacer domains to the carboxy-terminus of the Fc carrier domain. These 14 amino acid peptides have no sequence homology with native thrombopoietin.
Abbreviation: Fc, fragment crystallizable.

receptors and thereby affecting various immune responses.[67] Interaction with the Fcγ receptors may allow romiplostim to modify maintenance of humoral tolerance, cell maturation, antigen presentation, and Treg expansion. Finally, romiplostim may be capable of activating Tregs through two epitopes of the Fc region termed *Tregitopes*. Further exploration of these mechanisms in the function of peptibodies is warranted.[67]

Binding of romiplostim activates a wide range of signaling pathways that promote cell viability, cell growth, megakaryocyte endomitosis, megakaryocyte maturation, and importantly, platelet production (Figure 4).[3,59,68] Different TPO-RAs activate the TPO-R in different ways. For example, romiplostim activates the extracellular domain of the TPO-R, whereas eltrombopag and avatrombopag activate the transmembrane portion of the TPO-R (Figure 4),[3] which could lead to different levels of activity of the TPO-R and hence different responses within the stem cell and megakaryocyte compartments. Data from Broudy and Lin[59] and Currao et al[68] indicate that binding of romiplostim results in tyrosine phosphorylation and subsequent activation of Mp1, JAK2-STAT5, ERK1/2, and AKT downstream signaling pathways leading to gene transcription and increased megakaryocyte proliferation and differentiation. Similar to endogenous TPO, romiplostim stimulates growth of megakaryocyte colony-forming cells and increases megakaryocyte number, size, and ploidy.[59,60] Studies of platelets suggest that signaling in platelets was similar for romiplostim and eltrombopag; the role of intracellular iron chelation in the effect of eltrombopag is unique, but its clinical impact is not known.[3,69] Altogether, these characteristics of romiplostim clarify the reasons why it is a good treatment option for ITP and may be useful in other hematologic conditions that result in thrombocytopenia.

The pharmacokinetics and pharmacodynamics of romiplostim have been evaluated by Wang et al.[58,70] In brief, among healthy volunteers, platelet counts increased 1 to 3 days after intravenous administration and 4 to 9 days after subcutaneous administration, peaking on days 12 to 16.[58] Pharmacokinetics of romiplostim dosing is nonlinear and dependent on the dose administered and baseline platelet counts.[58,70] After subcutaneous administration at doses ranging from 3 to 15 µg/kg (an early upper limit of ITP dosing), peak serum concentrations of romiplostim occurred at approximately 7 to 50 hours posttreatment (median, 14 hours), and the half-life was approximately 1 to 34 days (median, 3.5 days).[5] Models suggest that romiplostim activity is driven by saturation of receptor occupancy on platelets and megakaryocytes rather than the romiplostim serum concentration.[71]

Clinical Evidence and Rationale for Use of Romiplostim in Chronic ITP

A large body of evidence supports the use of romiplostim to safely and effectively increase platelet counts in adults and children with ITP. Table 1 lists some key studies on the efficacy and safety of romiplostim in adult and pediatric patients with ITP. In adults, romiplostim increased platelet counts and reduced the rate of bleeding events in multiple Phase 1, 2, and 3 clinical trials for up to 52 weeks[61,62,72,73] and long-term extension studies or pooled analyses for up to 5.4 years.[63,74–76] In pediatric populations, platelet responses were observed up to 24 weeks in

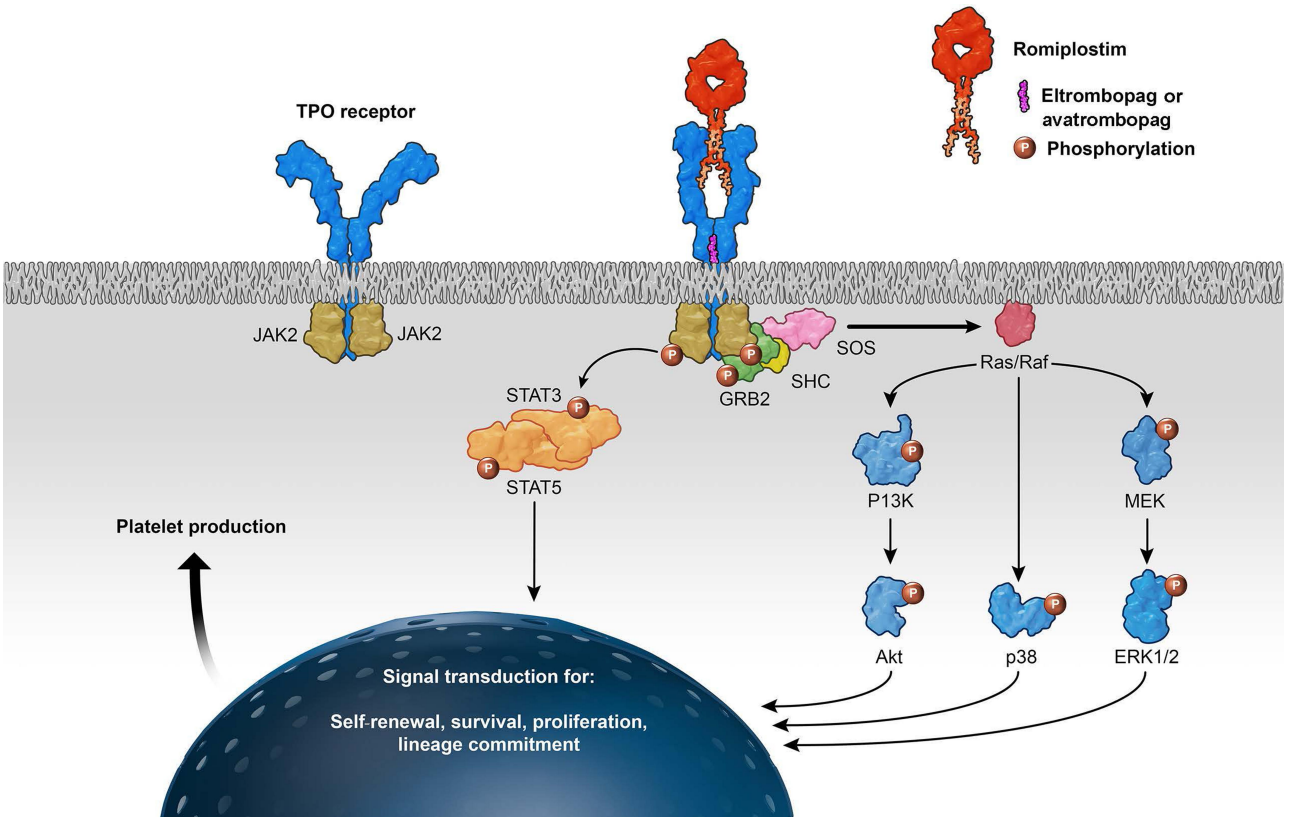

Figure 4 Cellular mechanism of action of thrombopoietin receptor agonists.[3] Binding of the ligand (TPO/TPO-RA) to the c-MPL receptor on the megakaryocyte causes conformational change in the receptor, resulting in downstream activation of the various signaling pathways, including JAK2/STAT5, PI3K/Akt, MEK/ERK, and p38, ultimately resulting in increased platelet production. Various pathways can be activated by the different substances. Romiplostim activates the extracellular domain of the TPO-R and eltrombopag and avatrombopag activate the transmembrane portion of the TPO-R.

Abbreviations: Akt, protein kinase B; ERK, extracellular-signal-regulated kinase; GRB2, growth factor receptor-binding protein 2; JAK, Janus kinase; MEK, mitogen-activated protein kinase/ERK kinase; MPL, myeloproliferative leukemia virus; P, phosphorylation; PI3K, phosphatidylinositol 3-kinase; Raf, rapidly accelerated fibrosarcoma kinase; Ras, rat sarcoma GTPase; SHC, Src homology collagen protein; SOS, Son of Sevenless; STAT, signal transducer and activator of transcription; TPO, thrombopoietin; TPO-RA, thrombopoietin receptor agonist.

clinical trials[77,78] and for up to 7 years in long-term extension studies.[79,80] In the extension study in pediatric patients with chronic ITP, romiplostim was associated with a treatment-free response (defined as a platelet count ≥50 × 10^9/L for ≥6 months with no ITP medications) in 15 patients (23%). Only one patient later experienced relapse at week 67 after about 30 weeks withholding romiplostim. The patient received romiplostim in weeks 68 to 96 and stopped all ITP treatments in weeks 97 to 99 per protocol. The patient had consecutive platelet counts ≥340 × 10^9/L.[79] Data from observational, real-world studies, which often describe effects on concomitant medications, such as corticosteroid dose reduction or discontinuation, have also shown that romiplostim often improved platelet counts and reduced bleeding events and hospitalizations in patients.[81,82] The efficacy and safety results were similar to those observed in clinical trials.[81]

Patients have also maintained sustained platelet counts after discontinuing romiplostim;[73,83–86] whether this is related to romiplostim or reflects spontaneous improvement of ITP is not known. Ghadaki et al found nine of 31 patients (29%) with ITP had sustained remissions, six of whom (19%) received romiplostim; in most of these cases, once platelet response was achieved, the medication was slowly tapered until it was successfully discontinued.[85] In a case series reported by Mingot-Castellano et al, four patients achieved sustained response (two of whom had chronic ITP), with the time to romiplostim taper and discontinuation ranging from 1 to 52 weeks and 14 weeks to 18 months, respectively.[86] Carpenedo et al found that 13 of 27 patients (48%, six of whom had chronic ITP) were able to discontinue romiplostim after a mean of 43.3 weeks of therapy; continued treatment-free response was maintained for a mean of 28.8

Table 1 Key Phase 3 and Long-Term Studies on the Efficacy and Safety of Romiplostim in Patients with Chronic and Early Stage ITP

Study Design	Study Details n, Duration	Weekly Initial Romiplostim Dose	Key Efficacy Results Romiplostim versus Comparator	Key Safety Results Romiplostim versus Comparator
Adults				
Phase 3 Two parallel, prospective, multicenter, placebo-controlled, double-blind[62]	125 Splen and Nonsplen (83 romiplostim; 42 placebo) 24 weeks	1 μg/kg	Overall platelet response Nonsplen 36/41 (88%) versus 3/21 (14%) for placebo Splen 33/42 (79%) versus 0/21 (0%) for placebo Durable platelet response Nonsplen 25/41 (61%) versus 1/21 (5%) for placebo Splen 16/42 (38%) versus 0/21 (0%) for placebo Reduced/discontinued concurrent therapy Romiplostim 20/23 (87%) versus 6/16 (38%) for placebo	Significant bleeding events Romiplostim 6/84 (7%) versus 5/41 (12%) for placebo No antibodies against romiplostim or TPO were detected
Phase 3 Multicenter, randomized, controlled, open-label[63]	234 Nonsplen (157 romiplostim; 77 SOC) 52 weeks	3 μg/kg	Response rate 2.3-fold higher for romiplostim versus SOC Treatment failure 18/157 (11%) versus 23/77 (30%) for SOC Splenectomy 14/157 (9%) versus 28/77 (36%) for SOC	Bleeding events 3.6 versus 5.0 per 100 weeks for SOC Serious AEs 35/154 (23%) versus 28/75 (37%) for SOC
Phase 3b Long-term, open-label, single-arm study[202]	407 Splen and Nonsplen 44 weeks (median)	1 μg/kg	Platelet response 370/407 (91%) achieved a platelet count ≥50 × 10^9/L that was at least double their baseline count	Treatment-related serious AEs 29/407 (7%); rate of 0.2 per 100 weeks Serious hemorrhagic events 32/407 (8%); rate of 0.4 per 100 patient-weeks
Long-term, open-label extension[75]	142 Up to 156 weeks (mean 69 weeks)	1 μg/kg or at dose received in parent study	Platelet response 124/142 (87%) at any time and during 67% of the weeks on study Discontinue/dose reduction concurrent treatment 16/32 (50%) and 11/32 (34%) reduced their dose by ≥25%	Treatment-related serious AEs 13/142 (9%) Severe bleeding events 12/142 (9%) Thrombotic events 7/142 (5%)
Long-term, open-label extension[74]	292 Splen and Nonsplen Up to 277 weeks (mean 110 weeks)	1 μg/kg or at dose received in parent study	Platelet response 95% at any time 97% Nonsplen and 90% Splen Maintained by all patients on a median of 92% of study visits	Treatment-related serious AEs 24/291 (8%); rate of 0.1 per 100 patient-weeks and no increase in frequency over time Bleeding events Rate of 2.8 per 100 patient-weeks (any bleeding event); most events were mild/moderate in severity Thrombotic events 19/291 (7%)

(*Continued*)

Table 1 (Continued).

Study Design	Study Details n, Duration	Weekly Initial Romiplostim Dose	Key Efficacy Results Romiplostim versus Comparator	Key Safety Results Romiplostim versus Comparator
Pooled analysis[76]	1111: Splen (395) and Nonsplen (716) Splen: Up to 281 (mean 87) weeks; Nonsplen: Up to 283 (mean 82) weeks	1 µg/kg Romiplostim exposure: 702 patient-years for Splen and 1130 for Nonsplen	Platelet response Splen: 310/376 (82%); 68% with sustained response Nonsplen: 592/648 (91%); 80% with sustained response	Treatment-related serious AEs (Splen versus Nonsplen) 9.3 versus 5.2 per 100 patient-years Hemorrhagic events (Splen versus Nonsplen) 266 versus 141 per 100 patient-years Thrombotic events (Splen versus Nonsplen) 6.3 versus 4.6 per 100 patient-years
Pediatrics				
Phase 3 Randomized, placebo-controlled[78]	62 (42 romiplostim; 20 placebo) 24 weeks	1 µg/kg	Platelet response 30/42 (71%) versus 4/20 (20%) for placebo Durable platelet response 22/42 (52%) versus 2/20 (10%) for placebo	Serious AEs 10/42 (24%) versus 1/19 (5%) for placebo Serious bleeding events 5/42 (12%) versus 1/19 (5%) for placebo No thrombotic events reported
Long-term extension[79]	65 Up to 7 years (median 2.6 years); 182 patient-years	1 µg/kg	Platelet response 61/65 (94%) at any time 47/65 (72%) for ≥75% of the time 38/65 (58%) for ≥90% of the time Treatment-free response (≥24 weeks) 15/65 (23%)	Serious AEs 19/65 (29%); 41 per 100 patient-years Serious bleeding events 7/65 (11%) No thrombotic events, fatalities, or new safety concerns with 182 patient-years of exposure to romiplostim
Early ITP				
Phase 2 Interventional, single-arm[73]	75 ITP diagnosed ≤6 months; median (IQR) ITP duration 2.2 (0.9, 4.3) months 12 months	1 µg/kg	Platelet response 70/75 (93%) during any 1 month Median (IQR) number of months with platelet response, 11 (8, 12) ITP remission 24 (32%)	Serious AEs 14 (19%); 3 (4%) treatment related Bleeding episodes 23 (31%); none were serious
Pooled analysis[102]	1037 (311 had ITP ≤1 year; 726 had ITP >1 year)	Mostly 1 µg/kg	Platelet response (ITP ≤1 year versus >1 year) Any: 238/277 (86%) versus 552/634 (87%) Durable: 147/277 (53%) versus 311/634 (49%)	Treatment-related serious AEs (ITP ≤1 year versus >1 year) 4 versus 7 per 100 patient-years Bleeding (ITP ≤1 year versus >1 year) 130 versus 182 per 100 patient-years Thrombotic/thromboembolic events (ITP ≤1 year versus >1 year) 4 versus 6 per 100 patient-years

Abbreviations: AE, adverse event; IQR, interquartile range; ITP, immune thrombocytopenia; Nonsplen, nonsplenectomized; SOC, standard of care; Splen, splenectomized; TPO, thrombopoietin.

months.[83] In a retrospective analysis, 11 of 46 patients (24%) with relapsed or refractory ITP who received treatment with a TPO-RA were able to discontinue treatment after achieving a platelet response; seven of the 11 patients (64%) received romiplostim for 2 to 36 months with a sustained response 16 to 54 months after discontinuation.[84] In their retrospective analysis, Lozano et al found that out of 121 patients who received TPO-RAs, 41 patients (34%) received romiplostim as their only TPO-RA (including 29 patients with chronic ITP).[87] Despite the intention of long-term treatment at its initiation, 23 patients (56%) tapered off romiplostim after different durations of treatment and were eligible for assessment of achieving treatment-free response (defined as maintaining a platelet count $\geq 50 \times 10^9$/L for at least 6 months without any ITP treatment); out of the 41 patients receiving romiplostim, 21 patients (51%) achieved treatment-free response. Of the 29 patients with chronic ITP, 13 patients (45%) achieved treatment-free response. These data reinforce that initiating romiplostim will not automatically require indefinite continuation of treatment, but rather, that a substantial fraction of patients will become and remain treatment-free with hemostatic counts.

Safety has been established for romiplostim treatment in patients with ITP for up to 5.4 years in adults and 7 years in children.[76,79] The most frequently reported adverse events among adult romiplostim recipients were headache and fatigue.[61–63,72–75] In a study in adults with ITP, two patients were diagnosed with hematopoietic malignancies (chronic lymphocytic leukemia in one patient; lymphoma in one patient who previously had peripheral leucocytosis); both patients had evidence of the disease prior to enrollment.[74] Reports of neutralizing antibodies to romiplostim were infrequent, with no antibodies to TPO detected in adults.[61–63,72–76] In a study in 65 children treated with romiplostim, neutralizing antibodies were detected after treatment in one patient (1.5%) who had left the study to start other treatment. Tests were negative on retesting 3 and 6 months later. No patients developed anti-TPO neutralizing antibodies.[79] In a study conducted by Wang et al in 245 patients with newly diagnosed ITP,[88] romiplostim did not result in neutralizing antibodies either to TPO or itself in adults with primary ITP. Alternatively, analysis of the pooled safety data from 14 trials (N=1059) that included pediatric (n=23) and adult (n=1036) patients revealed that three patients (ages not reported) developed neutralizing antibodies to romiplostim, but these did not cross-react with endogenous TPO. Surprisingly, there was no apparent clinical impact on romiplostim treatment in the one patient who continued treatment or in another patient who maintained platelet counts even though treatment had been discontinued. In the final patient, antibodies were detected at the end of the study.[89] In another long-term study assessing the efficacy and safety of romiplostim in children with ITP (N=203), 7 patients developed neutralizing antibodies to romiplostim; all discontinued treatment. In one patient who developed neutralizing antibodies to romiplostim, platelet counts decreased and rescue medicine was administered. Among the remaining patients, antibodies were detected ≥1 year after treatment started, and no reduction in therapeutic effect was reported. One patient developed neutralizing antibodies to TPO, which occurred 100 weeks after treatment started and romiplostim was continued for about 4 months after detection of neutralizing antibodies.[90]

In other studies, concurrent ITP medication use in adults was discontinued or decreased in responders with romiplostim use.[63,74,75] No randomized trial comparing romiplostim with placebo identified a significantly higher rate of thromboembolic events in patients treated with romiplostim; however, in a pooled analysis of 14 studies that included adults and children treated with romiplostim for up to 5.4 years, the rate of thrombotic events was 5.5 per 100 patient-years for both the romiplostim and placebo groups.[89] Therefore, the 5% rate of thrombotic/thromboembolic events in the long-term extension study of romiplostim being similar to the rate observed in an extension study of eltrombopag[75,91] suggests that an incremental prothrombotic effect of treatment with thrombopoietic agents exists.

Another area of interest is bone marrow reticulin, which has been shown to be increased in pediatric and adult patients receiving TPO-RAs.[92] In a pooled analysis of 13 studies, one of which included pediatric patients, 12 patients (1.8%) in the romiplostim group experienced bone marrow reticulin (1.3 events per 100 patient-years); all had received high doses of romiplostim (8–18 μg/kg/wk).[93] In another pooled analysis that included pediatric, adult, and geriatric patients, 17 cases of bone marrow reticulin and one case of collagen were reported among those receiving romiplostim compared with one case of reticulin in placebo recipients. Among the 10 patients for whom reticulin grading was reported, the highest grade of 4 was reported in one patient, grade of 3 in four, grade of 2 in two, and grade of 1 in three. Among patients who received romiplostim, the rate of bone marrow events

was 1.3 (18 cases) per 100 patient-years and 3.6 (6 cases) per 100 patient-years among patients on the highest dose (>10 μg/kg).[89] However, in a pooled analysis of adult patients from 13 studies treated for up to 5.4 years, the rate of increased bone marrow reticulin with romiplostim was low: 0.4/100 patient-years in splenectomized and 0.6/100 patient-years in nonsplenectomized patients.[76] The overall consensus of the studies is that an increase in reticulin in some patients with ITP treated with romiplostim occurs. However, levels of reticulin infrequently achieve a significant level (grade 3, the highest in the consensus scoring system) and rarely, if ever, appear to have any clinical effects. Increased reticulin appears to be reversible upon discontinuation of romiplostim.[94] It should also be noted that reticulin fibrosis has been incorrectly reported as myelofibrosis; the latter myeloproliferative disorder involves collagen fibrosis and not only reticulin, as seen with TPO agents.[89]

Clinical Evidence and Rationale for Use of Romiplostim in Newly Diagnosed and Persistent ITP

During the early phase of ITP, patients have an adaptive immune response, whereby autoimmunity is reversible (ie, increased production of proinflammatory cytokines, Th1 response) and autoreactive B-cell clones may be increased. It is during this period that encouraging treatment-free response may be possible. In contrast, late or progressive ITP is often associated with irreversible autoimmunity, as characterized by lasting cytokine imbalance, loss of immune tolerance, and the generation of difficult-to-target long-lived plasma cells.[95] Other events occurring in later stages of ITP that may justify the need for early intensive medical treatment include B-cell clonal expansion, antibody affinity maturation, epitope spreading, the functional diversification of autoantibody effector functions, and the generation of long-lived memory populations that differ from primary B cells.[96]

Newly diagnosed patients who received more intensive initial treatment regimens appeared to show improved initial and late response rates,[88,97–99] which is consistent with the theory that earlier treatment in any disease is potentially more curative than later treatment.

A Phase 3 study of dexamethasone with rituximab versus dexamethasone alone in newly diagnosed Italian adults with ITP showed that combination therapy improved 6-month sustained response (63%) compared with monotherapy (36%).[99] Similarly, in a phase 3 study in newly diagnosed Danish patients with ITP, the sustained response rate at 6 months was 58% with dexamethasone plus rituximab compared with 37% with rituximab alone. Also, a significantly longer time to relapse was observed for patients who received dexamethasone plus rituximab.[98] In a single-arm study of frontline dexamethasone plus eltrombopag in adults with ITP, 66.7% of patients experienced relapse-free survival at 12 months.[97] In a prospective, randomized study in adult Chinese patients with primary ITP, recombinant human TPO with high-dose dexamethasone versus high-dose dexamethasone monotherapy resulted in a higher incidence of early overall response (89.0% versus 66.7%, respectively; $P<0.001$), complete response (75.0% versus 42.7%; $P<0.001$), and sustained complete response at 6 months (46.0% versus 32.3%; $P=0.043$).[88]

Shorter ITP disease duration (≤1 year) has been shown to be a positive predictor of remission following romiplostim therapy.[100,101] Additionally, lower peak dose of romiplostim was an independent predictor of treatment-free response, suggesting that a better response intrinsically made a difference.[100]

One single-arm prospective study (referred to previously) investigated the use of romiplostim in patients with newly diagnosed and persistent ITP (adults with primary ITP duration ≤6 months) (Table 1).[73] In a Phase 2 study in which patients received romiplostim at a median treatment duration of 51 weeks, 24 of 75 patients (32%) maintained treatment-free platelet counts >50 × 10^9/L without the need for any ITP therapy for at least 6 months, following discontinuation of romiplostim at 1 year.[73] The platelet response rate in this 12-month trial was >90%, median time to first response was approximately 2 weeks, and cumulative median duration of response was 11 months.[73] Pooled data from nine romiplostim studies (N=1037) has shown that romiplostim may be more effective in achieving treatment-free remission in patients with ITP for <1 year compared with those with longer disease duration.[102]

A retrospective, long-term, multicenter follow-up study of 121 adults with ITP who had been treated with TPO-RAs assessed factors associated with treatment-free responses. Among patients in this retrospective study receiving only romiplostim (n=41) or eltrombopag (n=41), 95.1% in each group were not exposed to switching. Despite the small number of patients, the probability of achieving a treatment-free response was 3.2 times

higher among patients who only received romiplostim versus those who only received eltrombopag (P=0.014). Overall, 51.3% of patients who received romiplostim versus 24.4% of those who received eltrombopag were able to stop treatment. Among the 12 patients with newly diagnosed or persistent ITP at the start of treatment who received romiplostim only, 8 (67%) achieved treatment-free response (defined as maintaining a platelet count ≥50 × 10^9/L for at least 6 months without any ITP treatment).[87] Other single-arm studies have not confirmed this discrepancy.

It is possible that the (single) Fc domain could contribute to the rate at which romiplostim results in a treatment-free response. In addition to the potential immunomodulatory roles described earlier, the possibility that the Fc domain could drive immune tolerance, perhaps through induction of Treg cells,[103] needs to be studied further.

Clinical Evidence and Rationale for Use of Romiplostim Beyond ITP

Recent clinical evidence suggests a possible beneficial role of romiplostim in several disorders other than ITP that involve thrombocytopenia (Table 2).

Chemotherapy-Induced Thrombocytopenia

Chemotherapy-induced thrombocytopenia (CIT) is a common adverse effect of chemotherapeutic regimens that damage the bone marrow, depleting stem and progenitor cells and decreasing production of blood components pending restoration of the marrow. Chemotherapy agents can affect the megakaryocyte and platelet production pathway in different ways, such as affecting pluripotent stem cells or megakaryocyte progenitors, inhibiting nuclear factor kappa B, increasing the rate of platelet destruction by reducing Bcl-xL activity, or enhancing platelet clearance by immune mechanisms.[104]

It was estimated that nearly 10% of patients treated with chemotherapy experience clinically significant CIT during at least one cycle of their treatment.[105] Current management for CIT includes platelet transfusions, which are reserved for patients with severe thrombocytopenia.[104] Chemotherapy treatment delays and dose reductions are often used to manage CIT, which lead to reduced relative dose intensity and, consequently, reduced efficacy of the chemotherapy regimen.[106,107] A recent study investigated the effects of the antifibrinolytic drug tranexamic acid in preventing therapy-induced thrombocytopenia in patients undergoing treatment for hematologic malignancies; however, early results indicate that prophylactic tranexamic acid had no effect on the incidence of bleeding.[108] This suggests that a potential way to treat CIT is to increase platelet counts. Therefore, an unmet need exists for alternative treatment options for CIT to maintain chemotherapy dose intensity and treatment schedules.

The utility of romiplostim to prevent or treat CIT has been examined in preclinical studies,[109] case reports,[110,111] retrospective analyses,[112–114] and clinical studies.[115–117] Preclinical data from McElroy et al indicate that there is an inverse relationship between platelet counts and endogenous TPO concentration in mice subjected to chemotherapy/radiation therapy; romiplostim enhanced platelet recovery particularly when administered in high doses (≥100 μg/kg; an order of magnitude above the highest recommended dose in ITP of 10 μg/kg).[5,6,109] A phase 2 trial investigated romiplostim compared with observation in patients with solid tumors.[117] Because of promising results from an interim analysis that included a crossover part and lack of evidence that untreated control patients would experience corrected thrombocytopenia with additional time, the study was converted to a single-arm, open-label study after institutional review board approval; in 60 patients with solid tumors and thrombocytopenia, romiplostim was able to significantly increase platelet count, reverse CIT, and reduce the recurrence of CIT in approximately 85% of patients. Most patients who achieved platelet correction after receiving romiplostim were able to resume the same chemotherapy regimen that resulted in CIT.[117] In a study of 15 patients with hematologic (four patients) and nonhematologic (11 patients) malignancies undergoing chemotherapy, 13 (87%) achieved a platelet response, with 11 patients (73%) achieving platelet counts >100 × 10^9/L allowing continuation of full-dose chemotherapy.[115] There are several planned or ongoing studies in patients with CIT.[118–120] The optimal dosing regimen for romiplostim in the management of CIT will likely depend on the chemotherapy regimen being administered, the degree of platelet suppression expected, the time to reach the nadir, and the time to recovery of platelets. A multicenter study of romiplostim for CIT treatment in patients with solid tumors and lymphoid malignancies found a median optimized dose of 3 μg/kg for the entire cohort; the same median optimized dose was found for subcohorts of patients with solid tumors or hematologic

Table 2 Key Clinical Studies of Romiplostim in Various Clinical Disorders Other Than ITP

Study Type	Patients n, Attributes	Intervention Dose, Duration	Efficacy	Treatment-Related AEs	Key Interpretations
Chemotherapy-induced thrombocytopenia					
Prospective[115]	15, adults, nonhematologic cancer (n=11) and lymphoma (n=4) with postchemotherapy thrombocytopenia	Romiplostim: median (range) starting dose, 1 (1–3) μg/kg, median (range) maintenance dose, 3 (1–4) μg/kg; median (range) duration, 50 (7–322) days	87% achieved response 73% had platelet counts >100 × 10^9/L	No treatment-related toxicity and no hemorrhagic events reported	Romiplostim achieved an increase in platelet counts and enabled the continued use of full-dose chemotherapy in the majority of patients
Randomized comparison versus untreated observation; converted to open-label romiplostim arm[117]	60 (comparative arm: romiplostim, n=15; observation, n=8), adults with solid tumors and postchemotherapy thrombocytopenia despite reduction in dose and delay of chemotherapy	Romiplostim: starting dose 2 μg/kg weekly, increased by 1 μg/kg for up to 3 weeks, mean (range) dose, 2.6 (1.9–4.4) μg/kg weekly; duration of comparative arm, 3 weeks; open-label romiplostim continued for up to 34 months	In comparative arm, 93% of romiplostim patients achieved platelet counts ≥100 × 10^9/L within 3 weeks versus 12.5% of untreated patients Across all treated patients, 85% achieved platelet correction, 64% of whom resumed chemotherapy with same dose/regimen	10% of patients developed a VTE during first 12 months of treatment Romiplostim was not discontinued in these patients	Romiplostim is more effective than no treatment in correcting thrombocytopenia associated with chemotherapy; ongoing romiplostim can enable resumption of chemotherapy
Single-arm, multi-center study[121]	173 (153 with solid tumors, 20 with hematologic malignancy)	Open-label romiplostim, median (IQR) starting dose, 3 (2–3) μg/kg, weekly or intracycle for solid tumor; 3 (2–4) μg/kg, weekly or intracycle for hematologic malignancy	85% of all solid tumor patients achieved platelet count ≥100 × 10^9/L within a median of 9 days	21% of patients with solid tumors had chemotherapy intensity reductions and 11% of patients required platelet transfusions while on romiplostim	Romiplostim is effective for the management of CIT in patients with solid tumors, as demonstrated by improved platelet counts and low rates of chemotherapy dose reductions and treatment delays, bleeding, and platelet transfusions
Aplastic anemia					
Open-label, dose-adjustment, phase 2/3 clinical trial[131]	31, adults ineligible or refractory to immunosuppressive therapy	Romiplostim: 10 μg/kg weekly for 4 weeks, adjusted from 5–20 μg/kg; interim analysis at 1 year	84% had hematologic response at week 27 and 81% at week 53 Median days to response, 37.0; 75% achieved transfusion independence (week 53)	Headache, muscle spasms, ALT increased, fibrin D dimer increased, malaise, pain in extremity	Romiplostim appears effective and well tolerated in adults with treatment-refractory aplastic anemia

(*Continued*)

Table 2 (Continued).

Study Type	Patients n, Attributes	Intervention Dose, Duration	Efficacy	Treatment-Related AEs	Key Interpretations
Open-label, dose-finding phase 2 clinical trial, followed by long-term extension[18]	35, adults refractory to immunosuppressive therapy	Romiplostim: dose finding, 1–10 μg/kg weekly; extension study, 1–20 μg/kg weekly; up to 3 years	55% of evaluable patients had a platelet response at year 1 30% maintained platelet response at years 2 and 3	Myalgia, fatigue, dizziness	Romiplostim appears to stimulate proliferation of residual stem cells and progenitor cells in patients with refractory aplastic anemia
Perisurgical					
Single-center, retrospective study[149]	18, adults with pre-operative thrombocytopenia	Romiplostim: median (range) dose, 3 (1–7.5) μg/kg weekly; median (range) duration, 4.2 (0.6–50) weeks	All patients had an increase in platelet counts (median, 98 × 10^9/L) No surgical delays or cancellations due to thrombocytopenia	4 postoperative bleeding events 1 patient developed Foley catheter-associated clot after prostate surgery	Romiplostim effectively increases platelet counts in patients with thrombocytopenia to enable surgery, including major cardiac and orthopedic surgery
Single-center, retrospective study[148]	48, adults with preoperative thrombocytopenia	Romiplostim: median (range) starting dose, 3 (1–10) μg/kg weekly; median (range) duration, 13 (6–35) days	A platelet count ≥100 × 10^9/L achieved in 92% of patients after 3 doses of romiplostim, 79% after 2 doses, and 38% after a single dose	No apparent treatment-related AEs	Romiplostim rapidly increases platelet count in most thrombocytopenic patients preoperatively, to enable surgical (including cardiac, orthopedic, and neurosurgical) procedures to be undertaken safely and on schedule
Posttransplant					
Multicenter retrospective study of romiplostim and eltrombopag[162]	86 (romiplostim, n=35; eltrombopag, n=51), adults and children with persistent thrombocytopenia after allogeneic hematopoietic stem cell transplant	Romiplostim: starting (range) dose: 1 (1–7) μg/kg weekly, maximum (range) dose: 5 (1–10) μg/kg weekly Eltrombopag: starting (range) dose, 50 (25–150) mg/d, maximum (range) dose 75 (25–150) mg/d Median (range) duration, 62 (7–700) days	ORR for platelet recovery (≥50 × 10^9/L) in 72% of patients Median response at 66 (range, 2–247) days; response sustained after treatment discontinuation in 81% of patients	No patients discontinued treatment due to AEs Grade 3–4 liver abnormalities and fatigue observed in ~2% of patients	Romiplostim and eltrombopag appear effective in patients with isolated thrombocytopenia and those with secondary failure of platelet recovery posthematopoietic stem cell transplant

(*Continued*)

Table 2 (Continued).

Study Type	Patients n, Attributes	Intervention Dose, Duration	Efficacy	Treatment-Related AEs	Key Interpretations
Multicenter, prospective study[169]	24, adults with >7 days thrombocytopenia ≥45 days after allogeneic hematopoietic stem cell transplant	Romiplostim: dose escalation from 1–10 μg/kg weekly; median (range) dose, 5 (1–11) μg/kg weekly; duration, 12 weeks	18 patients achieved platelet count ≥50 × 10^9/L (without platelet transfusion) Median (range) time to response 45 (21–77) days; 16 patients had a durable platelet response	Bone marrow biopsies at 12 weeks and 1 year after the start of treatment did not show any increase in marrow fibrosis	Romiplostim appears to be effective in improving platelet count in patients with transfusion-dependent thrombocytopenia

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; CIT, chemotherapy-induced thrombocytopenia; IQR, interquartile range; ITP, immune thrombocytopenia; ORR, overall response rate; VTE, venous thromboembolism.

malignancy. Furthermore, romiplostim was found to be effective for the management of CIT in patients with solid tumors receiving various chemotherapy regimens.[121] Additional results of ongoing studies will help select the optimal dose of romiplostim in patients with CIT to minimize the chemotherapy delay or dose reduction, which may vary in efficacy according to the chemotherapy protocol and whether the bone marrow is involved by the malignancy. A meta-analysis of 16 studies examined the use of TPO-RA to either treat or prevent CIT in patients receiving chemotherapy. There was a significant reduction in chemotherapy dose delay or dose decrease, as well as a decrease in platelet transfusions, with TPO-RAs, with no apparent increased risk of thrombosis.[122] The primary question remains whether these important "practical" findings will translate into improved survival.

Aplastic Anemia

Acquired aplastic anemia is a clinical syndrome characterized by deficiency of red blood cells, neutrophils, monocytes, and platelets in the blood, as well as fatty replacement of the marrow with almost complete absence of hematopoietic precursor cells. Aplastic anemia does not usually have an evident cause but may be idiopathic or associated with an inciting agent. In either case, it is likely caused by cytotoxic T-cell autoreactivity that suppresses or destroys CD34+ multipotential hematopoietic cells.[123] Activated cytotoxic T cells secrete cytokines such as tumor necrosis factor-α and interferon-γ (IFN-γ) and increase nitric oxide synthase and nitric oxide production by marrow cells, leading to immune-mediated cytotoxicity and elimination of hemopoietic progenitor cells.[124] Studies have shown that patients with aplastic anemia have high levels of circulating TPO, with no correlation between TPO levels and platelet count, as well as a trend for higher TPO levels in patients with more severe aplastic anemia.[125–127]

Patients with aplastic anemia may be treated with immunosuppressants or receive a bone marrow transplant as part of first-line treatment.[128] Notably, the TPO-RA eltrombopag has been approved for the treatment of patients with severe aplastic anemia in the United States and the European Union.[128,129] Although not approved for use in aplastic anemia in the United States and the European Union, romiplostim is believed to similarly stimulate the proliferation of residual stem and progenitor cells in patients with aplastic anemia (approval has been received for refractory aplastic anemia in Japan and Korea).[18] Romiplostim has been shown to produce a trilineage response in patients with aplastic anemia, increasing platelets as well as erythroid and neutrophil responses.[18,130] For example, Lee et al conducted a multicenter phase 2 study with a randomized, parallel, dose-finding phase (8 weeks) followed by a long-term open-label extension in adult patients with aplastic anemia refractory to immunosuppressive therapy.[18] Of 35 patients in the study, all 10 patients who received romiplostim 10 μg/kg showed platelet responses, 30% of whom showed erythroid responses and 60% showed neutrophil responses during the first 8 weeks. At week 9, platelet response was achieved in 10 of 33 patients (30%) and appeared to be dose dependent, with responses in seven of 10 who received romiplostim 10 μg/kg and three of nine who

received romiplostim 6 μg/kg. Platelet responses at weeks 105 and 157 were maintained in 10 patients who received 3 to 20 μg/kg once weekly, and erythroid and neutrophil responses were observed in nine and five patients, respectively. A trilineage response was observed in five patients at weeks 53, 105, and 157. During weeks 53 to 157, dose tapering was permitted in patients with a stable platelet response, and three patients were able to discontinue romiplostim at 56, 483, and 490 days, respectively. Bone marrow cell assays also showed that improvement in platelet counts were associated with an increase in progenitor cells. Colony assay indicated that romiplostim influenced stimulation of primitive hematopoietic stem cells (CD34+ and CD38−) and enhanced differentiation of primitive hematopoietic stem cells to late progenitor cells.[18] Confirmation of these results was recently reported from a multicenter, phase 2/3, open-label study of 31 Japanese and Korean patients with aplastic anemia refractory to immunosuppressive therapy; results for romiplostim (initial dose 10 μg/kg for the first 4 weeks, which is then adjusted from 5 to 20 μg/kg thereafter) showed that 84% and 81% of patients achieved any hematologic response at weeks 27 and 53, respectively, and trilineage response was 39% at week 53. Finally, 75% of patients achieved transfusion independence by week 53.[131] Romiplostim is now being investigated in 2 registrational trials in Japan and Korea for frontline treatment of aplastic anemia in combination with cyclosporin A plus antihuman thymocyte immunoglobulin (NCT03957694) and cyclosporin A alone (NCT04095936).[132,133]

Three retrospective studies assessed romiplostim in patients with eltrombopag-refractory aplastic anemia. In a report of 8 patients with severe disease, only 1 (12.5%) responded to romiplostim (maximum dose, 10 μg/kg), achieving a trilineage response and remaining transfusion-independent after 21.2 months of treatment.[134] However, in the other two studies, which used a higher dose of romiplostim, response rates were better. Among 21 patients with severe disease, 16 (76%) achieved hematologic responses in ≥1 lineage at 3 months of romiplostim treatment (dose, 10–20 μg/kg), and 10 patients (48%) had a platelet response. Four patients (21%) achieved trilineage response at week 12. Among 10 patients who had been transfusion-dependent, two discontinued platelet transfusions, and three no longer required packed red cells.[135] Similarly, in another study of 10 patients (2 with severe disease) who switched to 20 μg/kg romiplostim, 7 (70%) achieved neutrophil, erythroid, or platelet responses, including one complete response, after median follow-up of 12 months.[136]

To explain why patients with severe aplastic anemia despite paradoxically high endogenous TPO levels are pancytopenic, it has been suggested that endogenous TPO forms a heterodimer with IFN-γ, preventing the TPO-R from heterodimerizing.[137] Specifically, IFN-γ is thought to bind to TPO and thus impair it from fully engaging the MPL receptor by disrupting the low-affinity binding site in a dose-dependent manner.[138] Eltrombopag does not interact with IFN-γ, but it binds to the TPO-R at a location distinct from the extracellular TPO binding site; thus, it is able to at least partially activate MPL signaling even in the presence of IFN-γ.[138–140] In theory, because romiplostim binds to the endogenous TPO site, it might not overcome the IFN-γ–mediated stem cell suppression resulting from TPO and IFN-γ heterodimer formation.[141] However, given that romiplostim has been shown to be clinically effective in signaling through the TPO-R in the high-IFN-γ state of severe aplastic anemia, romiplostim may either stoichiometrically overcome IFN-γ inhibition of endogenous TPO or else its mechanism is not affected by IFN-γ. Clarifying this mechanistic information will be useful to better understand its role in aplastic anemia.

Acute Radiation Syndrome

Romiplostim has been examined in mouse and macaque monkey models of acute radiation syndrome.[142–147] In a cell culture model, romiplostim in combination with IL-3 or IL-3 plus stem cell factor showed a strong regenerative effect on cell proliferation, megakaryopoiesis, thrombopoiesis, and megakaryocyte colony formation from X-irradiated CD34+ cells.[146] In mice subjected to total body irradiation at 70% lethal dose after 30 days, a single 30-μg/kg dose of romiplostim administered 24 hours after irradiation improved survival by 40% (57% versus 17% for control).[142] Similarly, Yamaguchi et al found that a 50-μg/kg romiplostim dose administered on 3 consecutive days starting within 2 hours of irradiation achieved complete rescue of mice exposed to lethal gamma irradiation.[143] They proposed that the ability of romiplostim to reduce lethality and pancytopenia may be due to multiple mechanisms, including stimulation of splenic progenitor cells, induction of pulmonary megakaryocytopoiesis, prevention of bone marrow cell death, modulation of DNA repair, and production of cytokines.

Romiplostim has also been examined in combination with granulocyte colony-stimulating factor and recombinant

human erythropoietin in irradiated mice, which led to 100% survival at day 30.[145] A study in a rhesus macaque model of acute radiation syndrome found that romiplostim alone or in combination with pegfilgrastim prevented severe thrombocytopenia and had other hematologic benefits.[147] Rhesus macaques were given a uniform dose of 550 cGy 24 hours before administration of saline (control), romiplostim, pegfilgrastim, or a combination of both. All animals showed clinical symptoms of acute radiation syndrome, including diarrhea, decreased appetite, hunched back, and petechiae, as well as significant reductions in neutrophils and platelets. Treatment with romiplostim or pegfilgrastim or both was associated with significantly improved survival compared with controls and reduced incidence of hunched back and petechiae. Neutrophils began decreasing 3 to 5 days post-irradiation in all groups and recovered most rapidly in those receiving pegfilgrastim (with or without romiplostim). In contrast, platelet counts declined beginning on day 5 post-irradiation but were overall less severe among the animals treated with romiplostim. The combination of romiplostim and pegfilgrastim resulted in the least severe thrombocytopenia and earliest recovery.[147]

Perisurgical

Romiplostim has been used successfully to increase platelet counts in patients with thrombocytopenia caused by different underlying pathologic conditions in association with various surgical procedures.[148–151] The underlying causes of thrombocytopenia included ITP, chronic liver disease, hematologic malignancy, and drug-related and hereditary causes. Retrospective data indicate that romiplostim can also improve platelet counts to levels conducive for performing various surgeries, including major cardiac, orthopedic, gastrointestinal, and neurologic surgeries.[148,149] In an early study, the median starting dose of romiplostim was 2.5 μg/kg; the median dose at the time of surgery was 3 μg/kg per week, with treatment starting approximately 4 weeks before surgery.[149] In a more recent study, the median starting dose of romiplostim was 3.0 μg/kg per week, and the median time to peak preoperative platelet count was 19 days.[148] Bleeding was infrequent, and most patients were able to continue with surgery on time and avoid platelet transfusions.[148,149] In the first randomized trial of perioperative management of ITP, eltrombopag was noninferior to intravenous immunoglobulin in terms of achieving and maintaining target platelet counts during the perioperative period.[152] However, it should be noted that for both romiplostim and eltrombopag, the amount of time needed before surgery to increase platelet counts could be problematic if a patient requires a procedure on a more immediate basis. The best treatment approaches under such circumstances (ie, TPO-RA versus intravenous immunoglobulin, dose, and timing of treatment) have been raised for the use of eltrombopag before and after surgery[153] and also need further consideration for romiplostim.

Posttransplant

Virtually all patients who undergo HSCT develop pancytopenia after the conditioning regimen, and persistent thrombocytopenia frequently occurs during the posttransplant course because platelets are the last blood component to recover. In certain patients, this thrombocytopenia never resolves (primary thrombocytopenia); in others, it resolves, but then recurs (secondary thrombocytopenia). Primary persistent thrombocytopenia is most prevalent with a cord blood transplant. Multiple causes contribute to post-HSCT secondary thrombocytopenia, after engraftment of megakaryocytes and achievement of an adequate platelet count, including decreased production and increased destruction, which may coexist.[154–156] Decreased production may be due to myelotoxicity of the conditioning regimen, poor graft function, rejection, graft versus marrow immunologic dysregulation (as a pattern of graft-versus-host disease), stromal damage, and viral reactivation. Increased platelet destruction is most often due to transplant-related microangiopathy, belonging to the umbrella of endothelial inflammatory diseases, which coincide to cause posttransplant thrombocytopenia.[157]

Thrombocytopenia post-HSCT can occur from secondary failure of platelet recovery, defined as a decline in platelet counts to below 20×10^9/L for 7 consecutive days or requiring transfusion support within 7 days after achieving platelet counts $\geq 50 \times 10^9$/L.[158] Long-lasting thrombocytopenia could lead to potentially lethal bleeding, thus necessitating the use of prophylactic or therapeutic platelet transfusions. A delayed platelet recovery has been associated with worse transplant outcomes.[159–161] Currently, there is a lack of proven effective and reliable methods to promote platelet engraftment and to prevent hemorrhagic complications and platelet transfusion needs.

Early in the post-HSCT course, patients often undergo multiple preemptive platelet transfusions to prevent bleeding complications. When engraftment is delayed, the use of a TPO mimetic may successfully increase platelet

counts. The response rate is significantly lower in patients with a decreased number of megakaryocytes before treatment.[162] No large prospective definitive studies have yet been reported. A few pilot and retrospective studies have suggested that romiplostim may be effective for improving platelet counts after HSCT.[163–165] In two small patient series, response to romiplostim was shown following HSCT in two of three patients[166] and in six of eight patients.[167] In a larger series, 100% of 20 patients treated with romiplostim achieved platelet engraftment at a median of 45 days following umbilical cord blood transplant compared with 85% of historical controls.[168]

The Spanish Group of HSCT retrospectively evaluated the safety and efficacy of TPO-RAs, either romiplostim or eltrombopag, in 86 patients with posttransplant thrombocytopenia.[162] The overall response rate for platelet recovery $\geq 50 \times 10^9$/L was 72% (median [range] response at 66 [2–247] days; median [range] treatment duration 62 [7–700] days), which was sustained in 81% of the responding patients after treatment discontinuation.[162] A prospective French phase 1/2 study enrolled 24 patients (10 with primary and 14 with secondary thrombocytopenia) providing weekly treatment with romiplostim (starting dose 1 μg/kg, escalating up to a maximum dose of 10 μg/kg).[169] Response, defined as platelet count $>50 \times 10^9$/L free of platelet transfusion, was achieved in 18 patients at a median (interquartile range [IQR]) time of 45 (29–41) days (range, 21–77 days), with a median (IQR) dose of 5 (4–6.8) μg/kg (range, 1–11 μg/kg); such a response was sustained in 16/18 patients for ≥8 consecutive weeks, independent of platelet transfusions.[169] Mahat et al[170] reviewed 12 studies (six case series and six case reports) involving the use of romiplostim for prolonged post-HSCT thrombocytopenia (primary thrombocytopenia in 17 patients and secondary in 32 patients); a platelet response of $>50 \times 10^9$/L free of platelet transfusion was observed in 40 out of the 49 patients (82%) overall.

There is less experience in children.[171–175] In particular, an Italian retrospective study recently reported on the use of eltrombopag in nine pediatric patients after HSCT; after a median treatment time of 36 days, eight of the nine patients (88%) achieved sustained platelet counts $>50 \times 10^9$/L.[173] In seven children with secondary failure of platelet recovery treated with romiplostim, six (86%) became transfusion-independent in the second week of treatment.[174]

These studies suggest romiplostim could be safely administered to patients with transfusion-dependent thrombocytopenia after allogeneic HSCT and may improve platelet counts. This is particularly relevant in the posttransplant setting when the risk of hemorrhagic events is often increased by diffuse endothelial damage. Whether treatment with romiplostim increases platelet counts and facilitates a bleeding-free window to allow spontaneous platelet recovery or in some way permanently increases the platelet count still needs to be assessed. The latter appears likely, however, in a number of the cases discussed previously.

In the setting of poor engraftment, which is characterized by persistently low platelet counts, often with trilineage involvement, and a hypocellular bone marrow examination, a stem cell boost of CD34+ selection of cells from the donor, also referred to as "top-up" transfusion, may be useful. The use of TPO-RA may allow additional time to delay the second graft request from donors and possibly observe platelet recovery without it.

Prospective studies are warranted to further investigate the role romiplostim may have in this setting. Post-HSCT complications, possibly contributing to thrombocytopenia, should be accounted for to properly assess the role of TPO-RA posttransplantation.

Other Settings

Experience with romiplostim in patients with inherited thrombocytopenia, such as myosin heavy chain 9-related disease (MYH9-RD)[176,177] and cases in which thrombopoietin mutation causes marked thrombocytopenia,[178,179] is limited to case reports. Eltrombopag showed efficacy in 11 of 12 patients with MYH9-RD.[180] Major responses were observed in eight patients (67%) and minor responses in three patients (25%). A more recent phase 2 study explored the effect of eltrombopag in 23 evaluable patients with expanded types of inherited thrombocytopenia (ie, MYH9-RD, ankyrin repeat domain-containing protein 26 [ANKRD26]–related thrombocytopenia, Wiskott–Aldrich syndrome/X-linked thrombocytopenia, monoallelic Bernard-Soulier syndrome, or integrin beta-3 [ITGB3]–related thrombocytopenia). All but two patients (8.7%) (ANKRD26-RT, n=1; ITGB3-RT, n=1) responded to treatment.[181]

There are no published studies on the use of romiplostim in patients with Wiskott–Aldrich syndrome/X-linked thrombocytopenia,[182] although anecdotal data suggest efficacy in five unreported cases, two from New York and three from Paris (personal communication). A recent case report of an atypical presentation of Wiskott–Aldrich

syndrome in an infant included the use of romiplostim and platelet transfusions to maintain platelet counts.[183] In a study of nine patients with Wiskott–Aldrich syndrome/X-linked thrombocytopenia, treatment with eltrombopag was found to be associated with beneficial effects on platelet count.[184] The study also found that platelet function and ability to be activated appeared to be relatively normal, and the increased bleeding tendency at a given platelet count was thought to be due to microthrombocytopenia rather than to intrinsic platelet abnormalities.[184] One patient in this study discontinued eltrombopag because of lack of response and switched to romiplostim and experienced a greater increase in platelet count and less bleeding.[184]

Patients with chronic liver disease often have thrombocytopenia, particularly those with cirrhosis.[185] In patients with advanced chronic liver disease, TPO declines as a result of splenomegaly and hepatic damage such that the liver cannot make even normal amounts of TPO. In the settings of accelerated platelet destruction and reduced platelet production, which are typical of advanced liver disease, this contributes substantially to the degree of thrombocytopenia.[151,185] Two TPO agents, avatrombopag and lusutrombopag, have been approved in the United States specifically to increase the platelet count in patients with thrombocytopenia and liver disease undergoing a procedure;[186,187] eltrombopag was previously approved to treat thrombocytopenia in patients with hepatitis C with liver disease to allow for the initiation and maintenance of interferon-based therapy.[129] Treatment with romiplostim was shown to improve platelet counts in a patient with hepatocellular carcinoma[188] and in patients with hepatitis C virus,[151] allowing most of these patients to undergo planned surgical procedures. In a case report of two patients with hepatitis C–related cirrhosis, treatment with romiplostim increased platelet counts and allowed the patients to complete an antihepatitis C protocol without dose delay or reduction, resulting in a sustained virologic response.[189]

A careful and thorough evaluation should be given before use of TPO-RAs in patients with thrombocytopenia and myelodysplastic syndrome (MDS) experiencing bleeding and requiring platelet transfusion. Several large randomized studies have been completed with both romiplostim and eltrombopag in patients with thrombocytopenia and MDS. Although neither romiplostim nor eltrombopag is approved for patients with MDS, treatment may improve platelet counts and reduce bleeding in a number of patients.[190] In one of the first of these studies, treatment with romiplostim compared with placebo initially was thought to increase leukemic blast levels in blood. The study was stopped because of the increase in blasts attributed to functional TPO-R on the cells. Although these initial concerns regarding the association of treatment with leukemic progression existed,[190–192] long-term follow-up of patients with MDS treated with romiplostim revealed no significant increases in the risk of acute myeloid leukemia or death.[193] Additional studies further explored the risk/benefit profile of romiplostim for the treatment of MDS;[191,194] however, concern for the risk of progression to leukemia has resulted in few trials in progress for this indication.[195–197] The initial study, with concern for increased blasts, was in patients with a low risk for MDS also being treated with decitabine,[198] whereas a later study in patients receiving romiplostim alone did not see this effect.[199] Currently, TPO agents can increase platelet counts, reduce bleeding, and decrease the need for platelet transfusions in certain populations of patients with MDS. However, even in the patients who achieve these responses, an extension of survival has not been shown.

Practical Treatment Considerations

Route of administration needs to be considered when choosing a TPO-RA. When patients are starting treatment, more frequent office visits are required until platelet counts are stabilized. Romiplostim administered by weekly subcutaneous injections[5] will result in such monitoring. Subsequently, the need for weekly injection may be a drawback. Home self-injections (available outside the US) may be an option for some patients and increase compliance, although some patients may prefer receiving treatment in an office by a healthcare professional.

Patients may often prefer oral TPO-RAs depending on the agent.[3] Avatrombopag, lusutrombopag (liver disease only), and eltrombopag are approved for oral administration.[129,186,187] Eltrombopag needs to be taken on an empty stomach (≥2 hours before or 4 hours after calcium-rich foods) and may not be suitable in patients with absorption problems, nausea, transaminitis, or irregular mealtimes.[3,129] Avatrombopag should be taken with food but does not have any dietary restrictions, and lusutrombopag can be taken with or without food.[186,187,200]

Discontinuation of romiplostim should be done in a stepwise fashion, as abruptly stopping treatment can lead to rebound thrombocytopenia in patients who

responded to treatment.[5,6,201] Platelet counts should be monitored at least weekly and for ≥2 weeks after discontinuation.[5,6] Additional therapy should be started if needed. The dose of romiplostim should be increased 1 μg/kg/week if platelet counts decrease to $<50 \times 10^9$/L or the patient exhibits symptoms.[5,6,201]

Discussion and Conclusions

Thrombopoietin is involved in multiple steps of platelet production, from the stem cell through development of mature megakaryocytes and possibly even platelet release.[10,11] Romiplostim is an important TPO-RA that has advanced treatment options for individuals with thrombocytopenia and acts by increasing platelet production and therefore increasing platelet counts. Increased platelet counts can reduce the need for platelet transfusions and decrease bleeding events in multiple conditions.[61–64] Romiplostim binds to and activates the TPO-R on megakaryocyte precursors,[58] activating multiple cell-signaling pathways, leading to enhanced cell growth and cell viability, which results in increased platelet production.[3,59,68] Although there are ample data on the use of romiplostim in adults and children with chronic ITP, evolving data on romiplostim in newly diagnosed patients with ITP shows its potential use as early treatment for adults who do not respond to corticosteroids. Furthermore, there is potential for either long-term or treatment-free responses in these patients with early-stage disease. The approval for romiplostim by the US Food and Drug Administration (but not EMA) was recently extended to cover this early use.[5] Studies have also shown romiplostim to be effective in improving platelet counts in various preclinical and clinical settings, including CIT, aplastic anemia, animal models of acute radiation syndrome, and liver disease. Although none of these indications have been approved yet in the United States, these studies highlight the versatility of romiplostim in thrombocytopenic conditions other than ITP. In particular, in severe aplastic anemia, for which eltrombopag has been licensed as upfront treatment in combination with standard immunosuppressive therapy, a recent study showed similar efficacy of romiplostim.[18] The safety and efficacy of romiplostim has led to anecdotal use in both primary and secondary thrombocytopenia in the post-HSCT setting, where response to treatment eventually allows prevention of bleeding and differentiation of thrombocytopenia caused by concomitant post-HSCT–specific complications. Although romiplostim cannot be recommended for use in unapproved clinical conditions, such as MDS or in other non-ITP patient populations, a positive risk/benefit profile has been established for the treatment of thrombocytopenia associated with chronic ITP. Future studies may expand this approval profile.

Abbreviations

ANKRD26, ankyrin repeat domain-containing protein 26; CIT, chemotherapy-induced thrombocytopenia; Fc, fragment crystallizable; HSCT, hematopoietic stem cell transplant; IFN-γ, interferon-γ; IL, interleukin; IQR, interquartile range; ITGB3, integrin beta-3; ITP, immune thrombocytopenia; MDS, myelodysplastic syndrome; MHCII, major histocompatibility complex class II; MPL, myeloproliferative leukemia virus; MYH9-RD, myosin heavy chain 9-related disease; Th1, type 1 T-helper; Th17, type 17 T-helper; TPO, thrombopoietin; TPO-R, thrombopoietin receptor; TPO-RA, thrombopoietin receptor agonist; Treg, regulatory T-cell.

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